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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/706,580	11/03/2000	Janet Cunningham	0800-0022	6169

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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/706,580	CUNNINGHAM, JANET	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 26-37* is/are pending in the application.

4a) Of the above claim(s) *1-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24 and 26-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Information Disclosure Statement

1. Reference AH-1 in the IDS filed 2/20/01 (but stamped as received on 4-18-02) has been crossed-out and will not be further considered as a part of that IDS since it was incompletely cited in the IDS and since it is the same Stratagene reference (Stratagene's Complete Control System for Inducible Mammalian Expression published in the Stratagene newsletter, Vol. 12, No. 1, first quarter, 1999, under the title of "Versatile Vectors for Ponasterone A- Inducible Control of Gene Expression in Mammalian Cells" by Denise Wyborski and Peter Vaillancourt (publication on http://www.stratagene.com/vol12_1/p1-4.htm)) cited in the Notice of References cited (PTO-892) with the Office action mailed 7/8/02. Applicant confirmed that the references were the same in a telephone conversation 3/17/03.

2. Applicant's election without traverse of Group V, in Paper No. 9 is acknowledged. The pending claims encompassed by the elected Group V are now claims 24 and 26-37.

Claims 1-23 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 9, filed 10/18/01.

3. Note the the following rejection is made in view of the amendments to the claims to make the claimed invention practiced *in vivo*. Applicant's response to the 35 U.S.C. 103 rejection in the previous Office action is moot in view of the following new grounds for rejection.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 24 and 26-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of transducing mammalian cells *in vitro* (in cells in cell culture) with the claimed AAV virions and the breath of methods of transducing mammalian muscle cells *in vivo* via intramuscular injection of the triple-combination of vectors AAV-Ecd1a-hEpo, AAV-CMV-EcR and AAV-CMV-RXR, does not reasonably provide enablement for methods of transducing mammalian cells *in vivo* (in a whole organism) with the breadth of vectors claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 24, 30 and 31 are drawn to methods for inducing gene expression in a mammalian cell *in vivo* via (1) transducing the mammalian cell with two AAV virion having different vectors-- one AAV vector comprising a transcriptional promoter region comprising at least one ecdysone-responsive element (EcRE), and a promoter capable of directing the *in vivo* transcription of said polynucleotide of interest in a mammalian cell, located downstream of the at least one EcRE; and the second AAV vector that comprises a coding sequence encoding an ecdysone receptor (EcR) and further comprises a coding sequence encoding a retinoid-X-receptor

(RXR), wherein said EcR and RXR coding sequences are operably linked to control elements capable of directing the in vivo transcription thereof in the mammalian cell; and (2) providing ecdysone, or an analog thereof capable of binding the EcR to said mammalian cell to induce the expression of the polynucleotide of interest; wherein the transcriptional promoter region comprises at least one enhancer, such as SP1.

Claims 26-29 and 32-34 are analogous to claims 24, 30 and 31, except, the mammalian cell is transduced with three vectors instead of two since the ecdysone receptor (EcR) and the retinoid-X-receptor (RXR) are encoded on different vectors.

Claims 35-37 are analogous to the above claims expect the transduced mammalian cell already comprises an RXR receptor and as such, the two vectors that are transformed into the cell are: (1) the first AAV vector comprising the transcriptional promoter region operably liked to a polynucleotide of interest, wherein the transcriptional promoter region comprises at least one ecdysone-responsive element (EcRE), and a promoter downstream of the at least one EcRE; and (2) the second AAV vector comprising a coding sequence encoding an ecdysone receptor (EcR) operably linked to control elements.

The specification as filed teaches by way of example the following:

In Example 1 on pages 29-33, the construction of the vectors used in Examples 2-5:

In Example 2, the AAV-Ecd1a-hEpo and AAV-Ecd1b-hEpo were transfected into ER-293 cells which have stably integrated EcR and RXR genes to test response to pon A regulation. The specification further teaches that "Figure 4A illustrates a dose response of pAAV-Ecd1a-

hEpo at 24-hours to pon A ranging from undetectable levels of Epo in the absence of pon A to over 2000 mU Epo in the high-dose group."

In Example 4, plasmids pAAV-CMV-RXR, pAAV-CMV-EcR and pAAV-Ecd1a-hEpo (or pAAV-Ecd1b-hEpo) were tested in C2C12 myotubes (muscle cells) in cell culture. Again, the presence of Epo was detected and measured.

In Example 5, the double vector cocktails (AAV-Ecd1a-hEpo and AAV-CMV-EcR) and triple vector cocktails (AAV-Ecd1a-hEpo, AAV-CMV-EcR and AAV-CMV-RXR) were delivered by injection into the tibialis anterior muscle of both hindlimbs of mice, followed by ponasterone A injection. The Epo expression was then measured in the blood. In the absence of inducer (Pon A), transgene expression was undetectable. Also, in the use of only the double-vector cocktail, no Epo was detected. However, Epo expression was detected with the use of the triple-vector cocktail. These results were from use of the ecdysone-analog, Pon A. The specification also states on page 38 that "Ecdysone-regulated expression of hEpo has also been demonstrated for over 60 days in immunocompetent mice."

The specification concludes that "[t]hese results suggest that ecdysone-regulated transgene expression is a viable option for treatment of beta-thalassemia and could potentially provide controlled gene therapy for a myriad of AAV applications including hematologic, metabolic, central nervous system, vascular disorders, cancer and other pathological states."

The claims as currently written specify that the methods of use of the claimed vectors are for the expression of any gene for use in any mammalian cell *in vivo*. The specification as filed

taught that the cocktail of two vectors was not functional *in vivo* although it had been functional in muscle cells *in vitro*. Therefore, the specification as filed provides unpredictability in the art for use of claims 24 and 35-37, which are drawn to methods comprising the two-vector system. Furthermore, there is a high level of unpredictability in the prior art for making and using any other AAV vectors as claimed, other than the triple cocktail taught in the specification as filed, for the methods of use *in vivo* due to the high level of unpredictability in the gene therapy art for design of any putative gene therapy vector.

Note Anderson who teaches on page 25, col. 2, lines 6-10, that "[t]he problems that investigators face in developing retroviral vectors that are effective in treating disease are of four main types: obtaining efficient delivery, transducing non-dividing cells, sustaining long-term gene expression, and developing a cost-effective way to manufacture the vector." Verma et al. state in the abstract that "[i]n principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged." They further state on page 239, col. 1, that "[a]lthough more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story." They further state that "[s]ometimes a clear definition of the target cell is needed. For example, the gene that is defective in cystic fibrosis has been identified, and clinical trials to deliver DNA as an aerosol into the lung have already begun. Although cystic fibrosis is manifest in this organ, it is still not clear that delivery of a correcting gene by this method will reach the right type of cell. On the other hand, to correct

blood-clotting disorders such as haemophilia, all that is needed is a therapeutic level of clotting protein in the plasma.... The choice of tissue in which to express the therapeutic protein will also ultimately depend on considerations such as the efficiency of gene delivery, protein modifications, immunological status, accessibility and economics." They further state on page 239, col. 3, that "[t]he Achilles heel of gene therapy is gene delivery. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression." Miller et al. further teach in the abstract that "[s]uccessful gene therapy requires not only the identification of an appropriate therapeutic gene for treatment of the disease, but also a delivery system by which that gene can be delivered to the desired cell type both efficiently and accurately. Reductions in accuracy will inevitably also reduce efficiency since fewer particles will be available for delivery to the correct cells if many are sequestered into nontarget cells. In addition, the therapy will have net benefit to the patient only if gene delivery is sufficiently restricted such that normal cells are left unaffected by any detrimental affects of bystander cell transduction."

Thus, there is a high level of unpredictability in the art for the design and use of vectors for expression of genes in a whole organism, as well as a high level of unpredictability that any tissue will be accessible to the route of delivery of the vector compound, and also there is a high level of unpredictability that any effect will be seen in the cells in a whole organism due to factors such as amount of gene product produced and sustained levels of the gene product. Thus, while the specification as filed enables the claims for expression of the specific vectors disclosed therein, the claims are not enabled for the broad scope claimed due to the high level of

unpredictability in the art at the time the invention was made and the absence of disclosure of specific substitutions to the disclosed vectors which are able to overcome the unpredictable hurdles *in vivo*. The specification as filed teaches delivery of the vectors to muscle tissue cells by direct injection. The instant claims are not enabled for delivery to other tissues via other routes of administration due to the high level of unpredictability in the art. As such, one of skill in the art would necessarily practice an undue amount of experimentation to make and use the breadth of vectors currently claimed.

6. The closest prior art was stated in the previous Office action as Stratagene's Complete Control System for Inducible Mammalian Expression published in the Stratagene newsletter, Vol. 12, No. 1, first quarter, 1999, under the title of "Versatile Vectors for Ponasterone A-Inducible Control of Gene Expression in Mammalian Cells" by Denise Wyborski and Peter Vaillancourt (publication on http://www.stratagene.com/vol12_1/p1-4.htm) in view of Natesan et al. (U.S. Patent 6,117,680) and Natesan (U.S. Patent6,015,709). This art is not considered to teach nor fairly suggest the enabled scope (see 35 U.S.C. 112, first paragraph, rejection above) of the instantly claimed invention.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

SEAN McGARRY
PRIMARY EXAMINER
1635

M. M. Schmidt
March 24, 2003